Clinical Utility of Procalcitonin in the Diagnosis of Pneumonia

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Abstract: BACKGROUND The clinical utility of procalcitonin in the diagnosis and management of pneumonia remains controversial. METHODS We assessed the clinical utility of procalcitonin in 2 prospective studies: first, a multicenter diagnostic study in patients presenting to the emergency department with acute dyspnea to directly compare the diagnostic accuracy of procalcitonin with that of interleukin 6 and C-reactive protein (CRP) in the diagnosis of pneumonia; second, a randomized management study of procalcitonin guidance in patients with acute heart failure and suspected pneumonia. Diagnostic accuracy for pneumonia as centrally adjudicated by 2 independent experts was quantified with the area under the ROC curve (AUC). RESULTS Among 690 patients in the diagnostic study, 178 (25.8%) had an adjudicated final diagnosis of pneumonia. Procalcitonin, interleukin 6, and CRP were significantly higher in patients with pneumonia than in those without. When compared to procalcitonin (AUC = 0.75; 95% CI, 0.71-0.78), interleukin 6 (AUC = 0.80; 95% CI, 0.77-0.83) and CRP (AUC = 0.82; 95% CI, 0.79-0.85) had significantly higher diagnostic accuracy (P = 0.010 and P < 0.001, respectively). The management study was stopped early owing to the unexpectedly low AUC of procalcitonin in the diagnostic study. Among 45 randomized patients, the number of days on antibiotic therapy and the length of hospital stay were similar (both P = 0.39) in patients randomized to the procalcitonin-guided group (n = 25) and usual-care group (n = 20). CONCLUSIONS In patients presenting with dyspnea, diagnostic accuracy of procalcitonin for pneumonia is only moderate and lower than that of interleukin 6 and CRP. The clinical utility of procalcitonin was lower than expected. SUMMARY Pneumonia has diverse and often unspecific symptoms. As the role of biomarkers in the diagnosis of pneumonia remains controversial, it is often difficult to distinguish pneumonia from other illnesses causing shortness of breath. The current study prospectively enrolled unselected patients presenting with acute dyspnea and directly compared the diagnostic accuracy of procalcitonin, interleukin 6, and CRP for the diagnosis of pneumonia. In this setting, diagnostic accuracy of procalcitonin for pneumonia was lower as compared to interleukin 6 and CRP. The clinical utility of procalcitonin was lower than expected. CLINICALTRIALSGOV IDENTIFIER: NCT01831115.

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Clinical Utility of Procalcitonin in the Diagnosis of Pneumonia

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BACKGROUND: The clinical utility of procalcitonin in the diagnosis and management of pneumonia remains controversial.

METHODS: We assessed the clinical utility of procalcitonin in 2 prospective studies: first, a multicenter diagnostic study in patients presenting to the emergency department with acute dyspnea to directly compare the diagnostic accuracy of procalcitonin with that of interleukin 6 and C-reactive protein (CRP) in the diagnosis of pneumonia; second, a randomized management study of procalcitonin guidance in patients with acute heart failure and suspected pneumonia. Diagnostic accuracy for pneumonia as centrally adjudicated by 2 independent experts was quantified with the area under the ROC curve (AUC).

RESULTS: Among 690 patients in the diagnostic study, 178 (25.8%) had an adjudicated final diagnosis of pneumonia. Procalcitonin, interleukin 6, and CRP were significantly higher in patients with pneumonia than in those without. When compared to procalcitonin (AUC = 0.75; 95% CI, 0.71–0.78), interleukin 6 (AUC = 0.80; 95% CI, 0.77–0.83) and CRP (AUC = 0.82; 95% CI, 0.79–0.85) had significantly higher diagnostic accuracy ($P = 0.010$ and $P < 0.001$, respectively). The management study was stopped early owing to the unexpectedly low AUC of procalcitonin in the diagnostic study. Among 45 randomized patients, the number of days on antibiotic therapy and the length of hospital stay were similar (both $P = 0.39$) in patients randomized to the procalcitonin-guided group (n = 25) and usual-care group (n = 20).

CONCLUSIONS: In patients presenting with dyspnea, diagnostic accuracy of procalcitonin for pneumonia is only moderate and lower than that of interleukin 6 and CRP. The clinical utility of procalcitonin was lower than expected.

SUMMARY: Pneumonia has diverse and often unspecific symptoms. As the role of biomarkers in the diagnosis of pneumonia remains controversial, it is often difficult to distinguish pneumonia from other illnesses causing shortness of breath. The current study prospectively enrolled unselected patients presenting with acute dyspnea and directly compared the diagnostic accuracy of procalcitonin, interleukin 6, and CRP for the diagnosis of pneumonia. In this setting, diagnostic accuracy of procalcitonin for pneumonia was lower as compared to interleukin 6 and CRP. The clinical utility of procalcitonin was lower than expected.

ClinicalTrials.gov Identifier: NCT01831115.

Pneumonia has diverse and often unspecific symptoms such as cough, fever, or dyspnea. In dyspneic patients, acute heart failure (AHF)[11] is another common underlying disorder and frequently occurs in parallel *(1, 2)*. Although the clinical introduction of natriuretic peptides as

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[11] Nonstandard abbreviations: AHF, acute heart failure; CAP, community-acquired pneumonia; CRP, C-reactive protein; BASEL V, basics in acute shortness of breath evaluation; ED, emergency department; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; AUC, area under the curve.

biomarkers has substantially facilitated the early diagnosis of AHF and their use is consistently recommended in both US and European clinical practice guidelines *(3–5)*, the role of biomarkers in the diagnosis of pneumonia is more controversial. For these reasons, early diagnosis and management of patients with pneumonia is often challenging.

In the absence of a large pivotal diagnostic study directly comparing the currently available inflammatory biomarkers, clinical practice guidelines differ in their recommendations. For instance, for the diagnosis of community-acquired pneumonia (CAP), British practice guidelines recommend C-reactive protein (CRP) *(6)*, whereas the American Infectious Diseases Society of America/American Thoracic Society guidelines favor procalcitonin *(7)*. Similar uncertainties relate to the use of procalcitonin in tailoring the duration of antibiotic therapy *(8–12)*.

To address these unmet needs, we aimed to perform 2 prospective studies to investigate the clinical utility of procalcitonin: first, a multicenter diagnostic study performed in patients presenting with acute dyspnea to ensure broad inclusion criteria enrolling as many pneumonia patients as possible to directly compare the diagnostic accuracy of procalcitonin with that of interleukin 6 and CRP; second, a randomized management study of procalcitonin guidance in patients with pneumonia and concomitant AHF *(13)*.

Methods

DIAGNOSTIC STUDY

Study design and study population. Basics in Acute Shortness of Breath Evaluation (BASEL V; ClinicalTrials.gov registry, number NCT01831115) was a prospective, multicenter, diagnostic study enrolling adult patients presenting with acute dyspnea to the emergency department (ED) of 2 university hospitals (Basel and Zurich, Switzerland). To enroll as many pneumonia patients as possible, acute dyspnea was the only criterion to be met, with no other additional symptom suggestive of pneumonia. Patients were included irrespective of renal function, except for patients with terminal kidney failure on chronic hemodialysis who were excluded. For this analysis, patients were not eligible if they had unavailable measurements of one or more investigated inflammatory biomarkers (procalcitonin, interleukin 6, CRP) at time of presentation.

The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committees. Written informed consent was obtained from all patients. The authors designed the study, gathered and analyzed the data according to the Standards for Reporting of Diagnostic Accuracy Group guidelines for studies of diagnostic accuracy (see Table 1 in the online Data Supplement), vouched for the data and analysis, wrote the paper, and decided to publish.

Adjudication of the final diagnosis. The final diagnosis of the illness causing shortness of breath was adjudicated by 2 independent cardiologist–internists who had access to all patients' medical records such as clinical history, physical examination, available laboratory findings, 12-lead electrocardiogram, chest x-ray, echocardiography, CT of the chest, microbiological findings, the response to therapy, and autopsy data for patients who died in hospital. All laboratory findings obtained through the clinician's routine diagnostic workup were available for the adjudicating physician. These findings were defined as internal measurements including one of the natriuretic peptides with class I recommendation [B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP)] *(4, 5)*, white blood cell count, and CRP. Physicians also were able to order procalcitonin at their discretion. Adjudicating physicians were blinded to measurements from study blood samples. These measurements were defined as external results including all interleukin 6 measurements and procalcitonin measurements in patients in whom the treating physician had not ordered procalcitonin as part of the clinical diagnostic workup. In situations of disagreement about the final diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist–internist.

Adjudicated pneumonia as primary end point. In cases of pneumonia, diagnosed according to criteria from Fine et al. and Leroy et al. *(14, 15)*, all cases of pneumonia were required to have a new infiltrate on chest x-ray or CT of the chest, in combination with microbiological proof of infection, or more than one of the major criteria. In cases of equivocal chest imaging (interstitial pattern, effusions), at least 2 major criteria were considered as necessary.

All patient records and discharge papers of patients with an adjudicated final diagnosis of pneumonia were reviewed to classify them into CAP, hospital-acquired pneumonia (HAP), or healthcare-associated pneumonia (HCAP) according to current practice guidelines *(16, 17)*.

Pneumonia with proven specific bacterial pathogen. In patients with an adjudicated final diagnosis of pneumonia, all available microbiological specimens and tests requested by the treating physician were centrally reviewed by an experienced internist. Results were interpreted in conjunction with consequential changes in antimicrobial therapy and the patient's clinical status. Therefore, in accordance with previous studies *(18)*, bacterial pneumonia was considered to be absent if one of the following conditions were met: an alternative

cause for pulmonary infiltrate was identified, only unspecific growth was found during microbiological testing, or the patient rapidly recovered without antimicrobial therapy. A microorganism was defined as a causative agent of pneumonia, if detected in blood, sputum, or bronchoalveolar lavage fluid culture or there was a positive urine diagnostic result for *Streptococcus pneumoniae* and *Legionella pneumophila* antigen. Only microorganisms cultured from representative sputum specimens according to Murray's criteria were considered *(19)*. Identical microorganisms found in more than 1 microbiological specimen or test in the same patients were considered only once.

Biomarker measurements. At each patient's presentation to the ED, blood samples were collected in tubes containing potassium EDTA. Internal measurements (all CRP, 2/3 of procalcitonin measurements) were requested by the attending ED physician and external ones (all interleukin 6, 1/3 of procalcitonin measurements) were gained from study blood samples, which were centrifuged and afterwards frozen at −80 °C until assayed in a blinded fashion in a dedicated core laboratory.

In the rare case of both measurements available for the same patient, the internal procalcitonin result was taken for analysis. Regardless of measurement type (internal or external), procalcitonin plasma concentration was quantified with the same automated sandwich immunoassay using a time-resolved amplified cryptate emission technology assay (PCT Kryptor®, B.R.A.H.M.S.) with a detection limit of 0.02 ng/mL and a functional assay sensitivity of 0.06 ng/mL, according to the manufacturer. The interassay coefficient of variation for concentrations >0.3 ng/mL was <6% *(10)*. CRP was measured with C-Reactive Protein Gen.3 immunoturbidimetric assay (Tina-quant®, Roche) on Roche/Hitachi cobas c systems. The assay's limit of detection was 0.3 mg/L with a functional assay sensitivity of 0.6 mg/L *(20)*.

Interleukin 6 was measured with the Erenna® immunoassay (Singulex) system, which used a microparticle immunoassay and single-molecule counting in a capillary flow system. The assay's limit of detection was 0.01 pg/mL, with lower and upper limits of quantification at 0.08 pg/mL and 50 pg/mL, respectively. Intraindividual variability and interindividual variation were 6% and 13%, respectively *(21)*.

RANDOMIZED MANAGEMENT STUDY

In a single-center study performed at the Instituto do Coração in Sao Paulo, Brazil, adult patients with AHF diagnosed in the ED who also had suspected pneumonia were randomized to procalcitonin guidance for determining the duration of antibiotic therapy or to the hospital's standard antibiotic treatment scheme (control).

All patients underwent procalcitonin testing and physical examination on day 0 (randomization) and day 5 after inclusion. Initially, all study physicians were blinded to procalcitonin measurements.

In the control group, duration of antibiotic therapy was determined by the treating physician blinded to procalcitonin plasma concentrations. For patients randomized to the intervention group, antibiotic therapy was maintained or suspended on day 5 by a well-trained study physician who was then unblinded to procalcitonin measurements directly after the plasma concentration was obtained from the inhouse Instituto do Coração Laboratory of Clinical Analyzes.

The decision whether to stop antibiotics was based on predefined procalcitonin cutoffs *(22, 23)*: antibiotic therapy was stopped if procalcitonin concentration was ≤0.25 ng/mL or with a decrease of >80% vs the concentration at randomization. At a procalcitonin plasma concentration of >0.25 ng/mL without substantial decrease, antibiotic therapy was continued in consultation with the treating physician. Procalcitonin concentration at admission had no effect on randomization or the decision to start antibiotic treatment.

The primary end point was the number of days on antibiotic therapy. Secondary end points included the duration of hospitalization, inhospital mortality, and the diagnostic accuracy of procalcitonin and CRP for pneumonia as adjudicated with CT of the chest. Further details regarding study population and statistical methods are described in the Methods section in the online Data Supplement.

Biomarker measurement. Laboratory parameters on hospitalized study patients such as complete blood count, urea, creatinine, CRP, and BNP were collected as part of the routine diagnostic workup prescribed by the treating physician. However, physicians were blinded to procalcitonin measurements derived from study blood samples. These were measured with a miniVIDAS® instrument (MS-10158120241, BioMérieux Clinical Diagnostics) with the VIDAS® B.R.A.H.M.S. PCT™ assay. The miniVIDAS system used enzyme-linked fluorescent assay technology, which combined the ELISA method with a final fluorescence reading. According to the manufacturer, 200 μL of heparinized plasma was sufficient, with a time to result of 20 min. The given measuring range was 0.05–200 ng/mL *(24, 25)*. All measurements were processed directly inhouse in the Instituto do Coração Laboratory of Clinical Analyzes.

STATISTICAL ANALYSES IN THE DIAGNOSTIC STUDY

ROC curves were constructed to assess the diagnostic accuracy of procalcitonin, interleukin 6, and CRP for pneumonia. Comparison of the areas under the ROC curve (AUCs) was performed as proposed by DeLong

Table 1. Baseline characteristics in the diagnostic study according to the presence or absence of pneumonia.[a]

	All patients (*n* = 690)	Non-pneumonia (*n* = 512)	Pneumonia (*n* = 178)	*P* value[b]
Demographics				
Age, years	74.0 (62.0–82.0)	74.0 (62.0–82.0)	74.5 (61.0–81.0)	0.987
Female sex	310 (44.9%)	239 (46.7%)	71 (39.9%)	0.137
BMI,[c] kg/m^2	25.7 (22.0–30.1)	25.8 (22.2–30.1)	24.9 (21.3–29.3)	0.183
Recent history				
Cough	482 (71.8%)	329 (66.5%)	153 (86.9%)	<0.001
Sputum production	346 (51.6%)	226 (45.7%)	120 (68.6%)	<0.001
Weight gain	138 (21.6%)	108 (23.1%)	30 (17.5%)	0.158
Clinical parameters at ED				
Systolic BP, mmHg	139.3 (±26.3)	141.6 (±26.9)	132.9 (±23.5)	<0.001
Diastolic BP, mmHg	80.7 (±18.0)	82.9 (±17.9)	74.43 (±16.6)	<0.001
Heart rate, bpm	94.0 (79.0–110.0)	92.0 (77.0–109.0)	97.0 (84.0–113.0)	0.011
Temperature, °C	37.4 (36.9–38.0)	37.3 (36.8–37.8)	37.9 (37.3–39.0)	<0.001
Pulse oximetry, %	95.0 (92.0–98.0)	96.0 (93.0–98.0)	94.0 (90.0–96.0)	<0.001
Respiratory rate, breaths/min	24.0 (18.0–28.0)	24.0 (18.0–28.0)	24.0 (18.0–32.0)	0.023
Rales	336 (50.1%)	220 (44.2%)	116 (67.1%)	<0.001
Increased JVP	132 (20.7%)	111 (23.4%)	21 (12.7%)	0.004
Edema	271 (40.0%)	220 (43.7%)	51 (29.3%)	0.001
History variables				
CRI	173 (25.1%)	128 (25.1%)	45 (25.3%)	1
CAD	225 (32.7%)	164 (32.1%)	61 (34.3%)	0.643
PAD	100 (14.9%)	74 (14.9%)	26 (15.1%)	1
COPD	299 (43.4%)	215 (42.1%)	84 (47.2%)	0.254
DM	163 (23.7%)	121 (23.7%)	42 (23.6%)	1
Dyslipidemia	268 (39.3%)	199 (39.3%)	69 (39.2%)	1
Hypertension	478 (69.6%)	359 (70.5%)	119 (66.9%)	0.394
MI	120 (17.5%)	88 (17.2%)	32 (18.2%)	0.818
Pneumonia	175 (25.7%)	109 (21.5%)	66 (37.5%)	<0.001
Smoker (current or ex-smoker)	484 (72.8%)	350 (71.3%)	134 (77.0%)	0.165
Immunsuppression[d]	100 (14.5%)	72 (14.1%)	28 (15.7%)	0.621
Outpatient medication				
Aspirin	241 (35.1%)	170 (33.4%)	71 (39.9%)	0.122
ACE inhibitors	220 (32.0%)	173 (34.0%)	47 (26.4%)	0.063
Aldosterone inhibitors	55 (8.0%)	45 (8.9%)	10 (5.6%)	0.201
ARB	114 (16.7%)	78 (15.4%)	36 (20.3%)	0.159
Beta blockers	270 (39.5%)	210 (41.5%)	60 (33.7%)	0.075
Calcium channel blockers	142 (20.7%)	96 (18.9%)	46 (25.8%)	0.054
Diuretics	349 (50.9%)	259 (51.1%)	90 (50.6%)	0.931
Antibiotics	71 (10.3%)	40 (7.9%)	31 (17.4%)	0.001
Laboratory parameters				
Hemoglobin, g/L	135.0 (122.0–148.0)	136.0 (122.0–150.0)	131.0 (119.0–142.0)	0.001
WBC, ×10^3/μL	10.2 (7.6–13.6)	9.4 (7.2–12.2)	12.6 (8.7–16.8)	<0.001

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Table 1. Baseline characteristics in the diagnostic study according to the presence or absence of pneumonia.[a]
(Continued from page 1535)

	All patients (*n* = 690)	Nonpneumonia (*n* = 512)	Pneumonia (*n* = 178)	*P* value[b]
Investigational parameters				
CRP, mg/L	23.3 (5.9–69.2)	13.2 (4.2–46.2)	96.6 (40.5–189.4)	<0.001
Interleukin 6, ng/L	15.5 (6.0–47.9)	10.6 (4.4–25.0)	54.7 (22.7–211.3)	<0.001
Procalcitonin, ng/mL	0.09 (0.05–0.19)	0.07 (0.05–0.14)	0.19 (0.09–0.63)	<0.001

[a] Continuous variables are presented as means with SD; for nonnormal distribution, as medians with interquartile ranges. For comparison, *t* test or Mann–Whitney *U*-test were used as appropriate. Categorical variables are shown as numbers and percentages. For comparison, Fisher's exact test was used.
[b] *P* value for comparison between non-pneumonia and pneumonia patients.
[c] BMI, body mass index; BP, blood pressure; JVP, jugular venous pressure; CRI, chronic renal insufficiency; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; MI, myocardial infarction; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; WBC, white blood cells count.
[d] Immunsuppression was defined as history of active cancer and/or chronic medication with ≥5 mg of oral prednisone or a dose equivalent.

(26). The sensitivity and negative predictive value of currently recommended rule-out cutoffs for inflammatory conditions were calculated *(27, 28)*. The percentage of patients eligible for rule out of pneumonia was used to quantify effectiveness. The effectiveness does not determine how many patients are correctly ruled out, it only shows the number of patients triaged toward rule out (given that the plasma concentration of the investigational parameters was below the cutoff) when presenting to the ED irrespective of whether they have the final diagnosis of pneumonia or not.

For nonnormally distributed data, correlations were assessed by Spearman's rank (r_s) correlation coefficient. In the diagnostic study, 6 subgroup analyses were predefined: in patients with only internal (that is, available for the adjudicating physician) measurements *(1)* or only external (that is, unavailable for the adjudicating physician) measurements *(2)* of procalcitonin to address the potential effect of inclusion bias; in patients with pneumonia and proven specific bacterial pathogen *(3)*; and in patients with final diagnosis of pneumonia with *(4)* or without *(5)* concurrent AHF. Furthermore, a sensitivity analysis including patients with at least 1 additional symptom suggestive of pneumonia (temperature ≥38.0 °C, cough, sputum production, or lung infiltrate) was performed *(6)*.

The interaction *P* values between the biomarker's AUC in the overall cohort and the biomarker's AUC in a specific subgroup were calculated with a logistic regression model for the prediction of pneumonia.

Statistical analyses were performed with SPSS for Windows 25.0 (SPSS Inc.), R statistical Software Version 3.4.3 (MathSoft), and MedCalc Version 17.9.7 (MedCalc, Software). All hypothesis testing was 2-tailed, and *P* values of <0.05 were considered to indicate statistical significance. Statistical analyses performed in the randomized management study are described in the Methods section in the online Data Supplement.

Results

DIAGNOSTIC STUDY

Patients: demographics and characteristics. Overall, 690 patients had the 3 inflammatory biomarkers measured and hence were eligible for the diagnostic analysis (see Fig. 1 in the online Data Supplement). These patients more often had symptoms and signs of pneumonia as compared to patients without these measurements (see Table 2 in the online Data Supplement). Median age was 74 years and 44.9% were women. AHF was the adjudicated final diagnosis in 311 patients (45.1%) and pneumonia in 178 patients (25.8%), with 58 patients (8.4%) adjudicated to have both AHF and concurrent pneumonia. Of 178 patients with an adjudicated final diagnosis of pneumonia, 150 (84.3%), 26 (14.6%), and 2 (1.1%) presented with CAP, HCAP, and HAP, respectively.

Inflammatory biomarkers. In our diagnostic study, CRP measurements were available for the adjudicating physician in all patients (100%), procalcitonin measurements in 453 patients (65.5%), and interleukin 6 measurements in no patient (0%). Procalcitonin, interleukin 6, and CRP were significantly higher in patients with pneumonia than in those without (Table 1). CRP and interleukin 6 ($r_s = 0.69$; $P < 0.001$) as well as CRP and procalcitonin ($r_s = 0.61$; $P < 0.001$) plasma concentrations were moderately correlated. Procalcitonin and interleukin 6 plasma concentrations also showed a moderate correlation ($r_s = 0.54$; $P < 0.001$). When compared to procalcitonin (AUC = 0.75; 95% CI, 0.71–0.78), interleukin

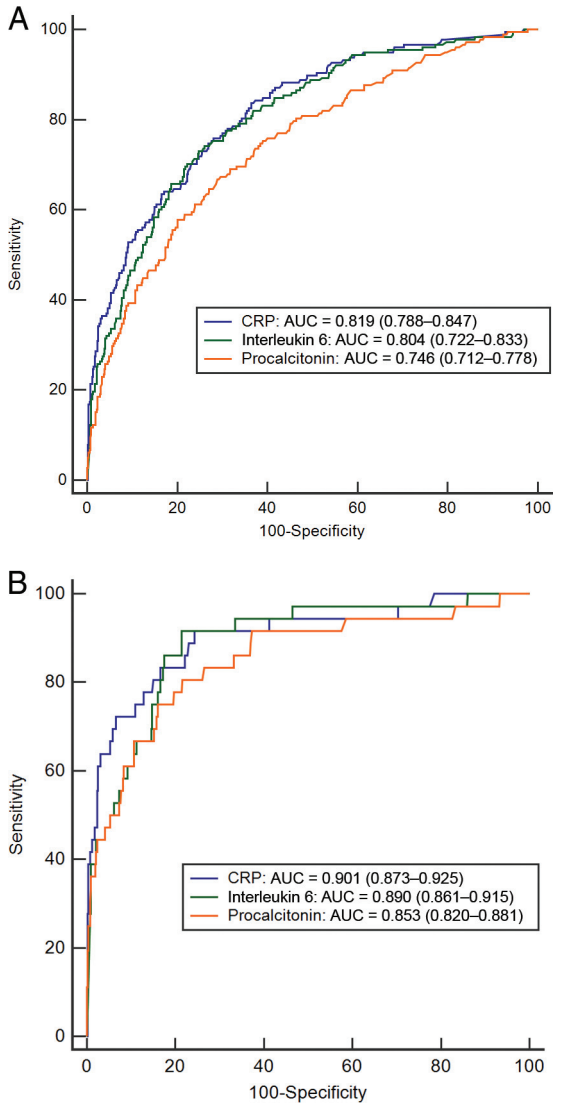

Fig. 1. Diagnostic accuracy of procalcitonin, interleukin 6, and CRP for the diagnosis of pneumonia (A) and pneumonia with proven specific pathogen (B) assessed by the AUC in the diagnostic study.

For (A), overall study population, n = 690; 178 patients thereof with adjudicated final diagnosis of pneumonia. For (B), third subgroup analysis, n = 548; 36 patients thereof with pneumonia and proven specific pathogen.

6 (AUC = 0.80; 95% CI, 0.77–0.83) and CRP (AUC = 0.82; 95% CI, 0.79–0.85) had significantly higher diagnostic accuracy ($P = 0.010$ and $P < 0.001$, respectively; see Table 3 in the online Data Supplement, Fig. 1A).

Subgroup analyses. Our findings were consistent in all predefined subgroups because there was no subgroup in which procalcitonin seemed to provide higher diagnostic accuracy (Fig. 2), including patients in whom procalcitonin measurements were available for the adjudicating physician (n = 452; see Table 4 in the online Data Supplement, Fig. 3A), patients with only unavailable procalcitonin measurements (n = 238; see Table 5 in the online Data Supplement, Fig. 3B), patients in whom microbiology workup was able to establish a specific bacterial (or fungal) pathogen (n = 36; see Tables 6, 7, 8, and 9 in the online Data Supplement, Fig. 1B), patients with a final diagnosis of pneumonia and concurrent AHF (n = 58; see Table 10 and Fig. 2A in the online Data Supplement), in patients with pneumonia only (n = 120; see Table 11 and Fig. 2B in the online Data Supplement), and in patients with additional symptoms suggestive of pneumonia (n = 545; see Table 12 and Fig. 3 in the online Data Supplement).

Performance of recommended cutoff concentrations. The performance of currently recommended cutoff concentrations for the rule out of pneumonia is summarized in Table 2. As an example, a procalcitonin concentration of 0.1 ng/mL or less provided a sensitivity of 71%.

RANDOMIZED MANAGEMENT STUDY

The management study was stopped early owing to the unexpectedly low AUC of procalcitonin in the diagnostic study. A total of 45 patients with AHF diagnosed in the ED who in addition had suspected pneumonia were eligible for randomization to intervention (procalcitonin guidance, n = 25) or control group (n = 20) (see Fig. 4 in the online Data Supplement). Baseline characteristics of the intervention and control group were similar (see Table 13 in the online Data Supplement). There was no significant difference in duration of antibiotic therapy and length of hospital stay between the procalcitonin-guided and standard group (Table 3). When comparing baseline characteristics of patients having antibiotic treatment stopped or continued in the procalcitonin-guided therapy group, one significant difference was found: left ventricular ejection fraction was significantly lower in patients having continued antibiotic therapy on day 5 (see Table 14 in the online Data Supplement).

Of 45 randomized patients, 30 (66.7%) underwent CT scan of the chest whereby pneumonia was radiographically confirmed in 19 patients (63.3%). At randomization (day 0), the diagnostic accuracy of procalcitonin and CRP for radiographically confirmed pneumonia as quantified by the AUC was 0.76 (95% CI, 0.57–0.90) and 0.89 (95% CI, 0.72–0.92; $P = 0.28$ for comparison), respectively (see Fig. 5 in the online Data Supplement).

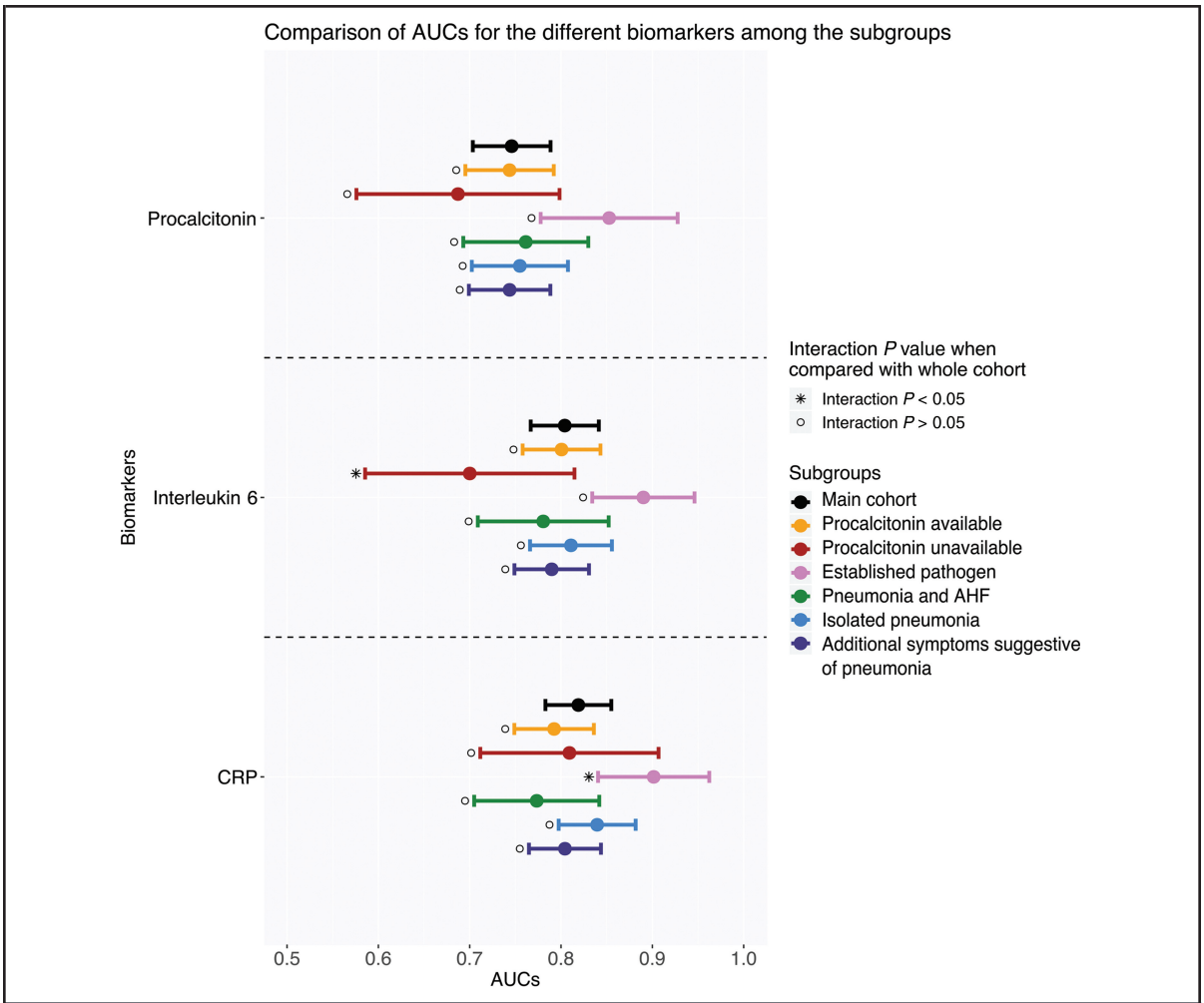

Fig. 2. AUCs within the overall study population and each subgroup for the assessed biomarkers in the diagnostic study.
The interaction *P* values were calculated when comparing the AUC achieved in the overall study population to the AUC in each subgroup.

Discussion

These prospective studies were performed to contribute to advancing the knowledge regarding the clinical utility of inflammatory biomarkers in the diagnosis and management of pneumonia. To the best of our knowledge, the diagnostic study is the first direct comparison of procalcitonin, CRP, and interleukin 6 against a reference standard based on central adjudication by 2 independent experts. We report 4 major findings.

First, in our diagnostic study in patients presenting with acute dyspnea to the ED, when evaluated against a final adjudicated diagnosis by 2 independent experts based on current guidelines, the diagnostic accuracy of procalcitonin for pneumonia was only moderate (AUC 0.75). As procalcitonin concentrations were available to both clinicians and adjudicators in two-thirds of the patients, this point estimate likely may slightly overestimate the true diagnostic accuracy of procalcitonin. This finding is in full agreement with an AUC of 0.72 observed in a similar diagnostic study using central adjudication with complete blinding to procalcitonin *(8)*. Second and likely of most importance, CRP and particularly interleukin 6, which was blinded in all patients, provided significantly higher diagnostic accuracy when directly compared to procalcitonin for the early diagnosis of pneumonia. This finding is supported by observations made in a large diagnostic study performed in primary care with 2820 patients presenting with acute cough, of whom 140 (5%) had pneumonia. CRP, but not procalcitonin, increased the diagnostic accuracy for pneumonia when added to the clinical information *(29)*. Similarly, 2

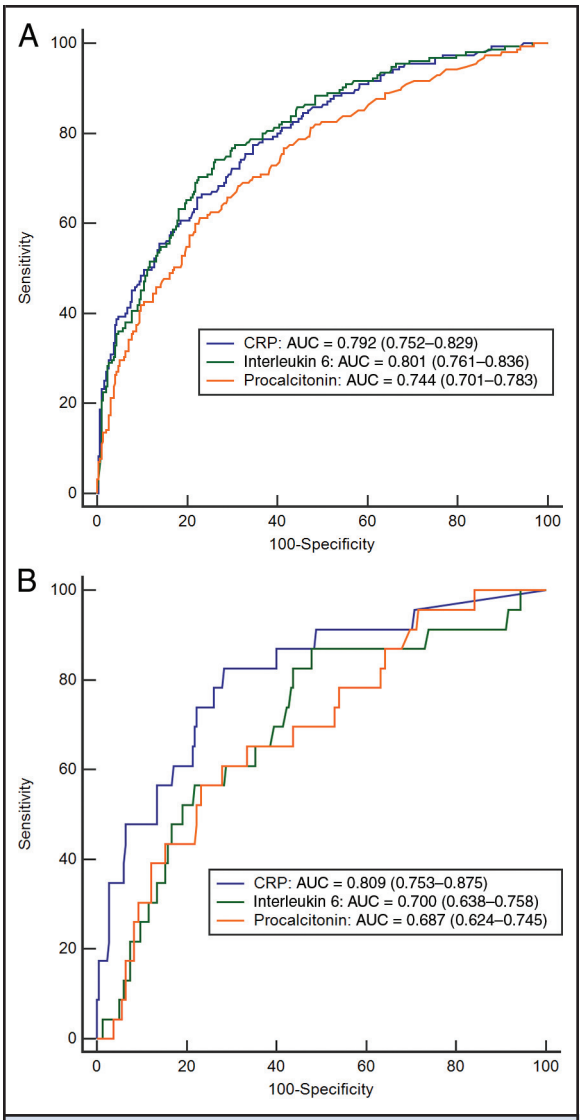

Fig. 3. Diagnostic accuracy of interleukin 6, procalcitonin, and CRP for the diagnosis of pneumonia assessed by the AUC in case of procalcitonin available (A) and unavailable (B) for the adjudicating physician in the diagnostic study.

For (A), first subgroup analysis, n = 452; 155 patients thereof with adjudicated final diagnosis of pneumonia. For (B), second subgroup analysis, n = 238; 23 patients thereof with adjudicated final diagnosis of pneumonia.

small single-center studies observed even slightly higher diagnostic accuracy for CRP vs procalcitonin for the differentiation of CAP vs exacerbation of asthma or chronic obstructive pulmonary disease *(30, 31)*.

In contrast, a single-center study enrolling 101 patients admitted to a medical intensive care unit found a higher diagnostic accuracy for Procalcitonin than for CRP and interleukin 6 for sepsis. This discrepancy may at least in part be explained by the higher prevalence of sepsis with established bacterial origin in that study than in our diagnostic study *(32)*.

Given the fact that the cost of measuring CRP in most countries is <5% of that of procalcitonin, these data suggest that the current American Infectious Diseases Society of America/American Thoracic Society guidelines favoring procalcitonin may need to be revised and CRP or interleukin 6 should be considered the inflammatory biomarker of choice, complementing clinical and radiographic assessment in the early diagnosis of pneumonia *(7)*. As CRP available and interleukin 6 unavailable to the adjudicating physician provided a similar AUC in the diagnostic study, it is likely that the true diagnostic accuracy of interleukin 6, which is secreted earlier than CRP in response to bacterial infection *(33)*, is even higher than that of CRP. Future studies ideally with blinded measurements of both biomarkers are warranted to either confirm or reject this hypothesis. Third, in the randomized management study of AHF patients who in addition had suspected pneumonia, procalcitonin guidance of the duration of antibiotic therapy resulted in comparable duration of antibiotic therapy and length of hospital stay. This finding is supported by a recent much larger randomized study also showing no benefit of procalcitonin guidance when compared against a contemporary standard of care *(12)*. In contrast, a subgroup analysis of patients with a history of chronic heart failure enrolled in a randomized procalcitonin-guided antibiotic stewardship trial found evidence of clinical benefit in patients with low procalcitonin concentration *(11)*. Fourth, in the diagnostic part of the randomized management study with a CT scan as the reference standard, again the diagnostic accuracy of procalcitonin was only moderate (AUC, 0.76).

Overall, these findings corroborate and extend previous studies on procalcitonin *(8, 18, 29–31, 33)* and help to put the seemingly contradictory conclusions into perspective. A single low procalcitonin concentration in patients presenting with suspected pneumonia to the ED should not be used in isolation to withhold potentially life-saving antibiotic therapy. Unfortunately, this has become clinical practice in some institutions, although scientifically incorrect. First, the findings of this study clearly indicate that the diagnostic accuracy of procalcitonin is insufficient for this clinical consequence. Second, previous open-label randomized controlled trials evaluating procalcitonin guidance in combination with the standard of care (always including CRP) did not withhold antibiotic therapy based on a single measurement in isolation but initiated antibiotic therapy in all patients and stopped it after about 12 h in patients with persistently low procalcitonin concentration and clinical stability *(9–11)*. Given the well-documented time delay in the rise in

Table 2. Performance of currently recommended cutoff concentrations for the ruleout of pneumonia in the diagnostic study.

Biomarker	Plasma concentration	Sensitivity	Negative predictive value	Effectiveness[a] (Percentage fulfilling criteria, n)
Procalcitonin	<0.1 ng/mL	0.71 (0.64–0.78)	0.87 (0.83–0.90)	55.0% (380)
Interleukin 6	<15 ng/L	0.83 (0.77–0.88)	0.91 (0.88–0.94)	49.6% (342)
CRP	<10 mg/L	0.93 (0.88–0.96)	0.95 (0.91–0.97)	34.2% (236)

[a] The effectiveness shows the number of patients triaged toward ruleout (given the plasma concentration was below the mentioned cutoff) when presenting to the ED irrespective of final diagnosis of pneumonia.

systemic concentrations of procalcitonin and CRP, this is an essential difference, particularly in patients presenting early after symptom onset *(6, 17)*. In full agreement with this concept, the results of this study document that established low cutoffs for both procalcitonin and CRP do not have sufficiently high negative predictive value to reliably exclude CAP in general and pneumonia with proven specific bacterial pathogen in particular.

For the second possible clinical consequence, shortening the duration of antibiotic therapy, it is important to highlight that some, but not all, open-label randomized controlled trials evaluating procalcitonin guidance in combination with the standard of care (always including CRP) vs the local standard of care were able to show a reduction in days on antibiotics *(9–11, 34, 35)*. In general, procalcitonin guidance was able to reduce the number of days when the standard of care tended to include rather long durations of treatment with poor stewardship, but not when compared against a contemporary standard of care with strict stewardship.

Several limitations merit consideration when interpreting our findings: first, no specific sample size calculation was performed for this secondary analysis of BASEL V. Although this is one of the largest diagnostic studies with central adjudication by 2 independent experts performed until now, it might have been underpowered for some comparisons. Second, although we used one of the most stringent methods to adjudicate for the presence or absence of pneumonia including central adjudication, we may still have misclassified a small number of patients. However, this misclassification would have resulted in an underestimation of the true AUCs of all biomarkers examined and could not explain the significantly higher AUC observed for blinded interleukin 6 as compared to procalcitonin mostly available to the adjudicating physician. Third, we cannot generalize our findings to patients with terminal kidney failure requiring dialysis because these patients were excluded. Fourth, the randomized management study was stopped prematurely and therefore has limited statistical power.

In conclusion, in patients presenting with dyspnea, diagnostic accuracy of procalcitonin for pneumonia is only moderate and lower than that of interleukin 6 or

Table 3. Primary and secondary endpoints in the overall study population and in patients randomized to intervention in the randomized management study.[a]

Endpoints	Overall study population (n = 45)	Intervention (n = 25)	Control (n = 20)	P value[b]
Duration of antibiotic treatment, days	10.5 (6.8–13.0)	10.5 (6.0–12.2)	10.5 (8.8–13.2)	0.387
Duration of hospital stay, days	11.5 (6.0–22.5)	10.0 (6.0–18.2)	14.0 (6.8–24.2)	0.388
Inhospital mortality, n (%)	9 (20.5)	5 (20.8)	4 (20.0)	1.000

Endpoints	Patients randomized to intervention (n = 25)	Antibiotic therapy sustained (n = 15)	Antibiotic therapy stopped (n = 10)	P value[c]
Duration of antibiotic treatment, days	10.5 (6.0–12.2)	12.0 (11.0–14.5)	6.0 (6.0–6.0)	<0.001
Duration of hospital stay, days	10.0 (6.0–18.2)	16.0 (8.5–27.0)	6.0 (5.0–6.0)	0.004
Inhospital mortality, n (%)	5 (20.8)	4 (26.7)	1 (11.1)	0.697

[a] Continuous variables are presented as medians with interquartile ranges and categorical variables as numbers and percentages. For comparisons, Mann–Whitney U or chi-square tests were used as appropriate.
[b] P value for comparison between intervention and control group.
[c] P value for comparison between antibiotic therapy sustained and stopped group.

CRP. Overall, the clinical utility of procalcitonin was lower than expected.

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